## REMARKS

Reconsideration of the present application is respectfully requested. Claims 17-26 are currently pending. Claim 17 is amended to more particularly state the invention; the amendment does not constitute new matter. Claims 1-16 have been previously canceled without prejudice. No new matter has been introduced into the present application.

## I. Rejections under 35 U.S.C. § 102(b)

U.S. Patent No. 5,165,938 to Knighton

Claims 17-21 stand rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,165,938 to Knighton (hereafter, "Knighton"). The Examiner contends that Knighton discloses a topical drug composition for wound healing, produced from blood, comprising microparticles released by collagen and/or thrombin activated platelets into a liquid medium. The Examiner further alleges that the microparticles are separated from the platelets by centrifugation, and mixed with microcrystalline collagen and frozen. Thus, according to the Examiner, the composition of Knighton includes microparticles and extracellular matrix, which allegedly anticipates the claims.

Applicants submit that the claims are directed to a therapeutic composition for promoting wound healing comprising effective amounts of microparticles and one or more added extracellular matrix material, wherein the microparticles are prepared by, among other steps, separating the microparticles from an aqueous fraction of a thrombocyte-free liquid medium.

Applicants submit that Knighton does not anticipate the pending claims because the reference does not disclose all the elements of the claims. In particular, Knighton does not disclose a composition comprising microparticles prepared by separating the microparticles from an aqueous fraction of a thrombocyte-free liquid medium.

Rather, Knighton describes adding thrombin to platelet-rich plasma, whereby the platelet-rich plasma is coagulated and fibrinogen is transformed into insoluble fibrin. Knighton separates the fibrin by centrifugation and discards the fibrin containing sediment. Knighton then mixes the supernatant with a macromolecular substance such as microcrystalline collagen to obtain a paste, which can be applied to wounds. *See, e.g.,* Knighton at Col. 3, line 15-Col. 4, line 6. According to Knighton, the supernatant that is mixed to form a paste for use as a therapeutic

composition includes platelet-derived growth factor (PDGF) and platelet-derived angiogenesis factor (PDAF). *See,* Knighton at Col. 3, lines 60-68.

The Examiner contends that the pending claims are product-by-process claims, and the properties of the claimed product are not materially or functionally different than the product disclosed by Knighton. Thus, according to the Examiner, the "aqueous fraction" present in Knighton's product, but not the claimed product, does not patentably distinguish the pending claims. *See,* the Final Office Action at pages 7-9.

The Examiner states that the specification as filed provides no specific definitions about the chemical nature/structure or molecular weight of the claimed microparticles. *See,* the Final Office Action at page 8. As discussed in the previous response, and not by way of concession, and solely for the sake of argument, Applicant submits that the claimed composition comprising microparticles and the composition of Knighton are different products due to their different processes of production.

> The structure implied by the process steps should be considered when assessing the patentability of product-by-process claims over the prior art, especially where the product can only be defined by the process steps by which the product is made, or where the manufacturing process steps would be expected to impart distinctive structural characteristics to the final product.

*See, e.g., In re Garnero,* 412 F.2d 276, 279, 162 USPQ 221, 223 (CCPA 1979); and M.P.E.P § 2113. The process described by the pending claims is different than the process described by Knighton, and as such, the products prepared according to the two processes are different. For example, by separating the microparticles from an aqueous fraction of a thrombocyte-free liquid medium, as recited by the pending claims, the presently claimed invention provides for a composition comprising microparticles and one or more added extracellular matrix material that can be combined together in a defined ratio.

The Examiner contends that Knighton describes a platelet rich plasma ("PRP") that is activated with thrombin, whereby the activated platelets release microparticles. According to the Examiner, the PRP is then subjected to a removal of platelets and fibrin by centrifugation to produce a supernatant that is the claimed "thrombocyte-free liquid medium" which "aqueous fraction" contains PDAF and PDGF or alpha granules with PDAF and PDGF. Applicant respectfully disagrees with the Examiner's characterization of the methods of

Knighton. The therapeutic composition of Knighton is produced according to the following steps:

1. Blood is stabilized and centrifuged to obtain a platelet-rich plasma (PRP) with a high concentration of platelets. *See,* Knighton at Col. 2, lines 20-30; and Col. 3, lines 33-38.
2. Thrombin is added to the PRP to activate the platelets. The thrombin activated platelets release PDGF and PDAF. The activity of the thrombin coagulates the fibrinogen. The PRP is then subjected to a removal of platelets and fibrin by centrifugation. The resulting supernatant contains both PDAF and PDGF, and the pellet is discarded *See,* Knighton at Col. 2, lines 30-36; and Col. 3, lines 49-52.
3. In order to apply the platelet-free supernatant containing PDGF and PDAF to a wound, it is preferably added to a biologically compatible macro-molecular substance which acts as a carrier. *See,* Knighton at Col. 2, lines 39-59; and Col. 3, lines 1-4.

In contrast to the pending claims, Knighton activates platelets in PRP with thrombin, separates thrombocytes from the PRP, and then combines the platelet-free activated PRP supernatant with a carrier. Knighton does not suggest or describe an additional step of separating microparticles from an aqueous fraction of a thrombocyte-free liquid medium by a method selected from the group consisting of differential centrifugation, filtration and affinity chromatography. As such, the supernatant of Knighton would therefore contain proteins and other cellular debris that was not removed with the coagulated plasma and fibrin. Knighton provides no guidance with regard to the amount of microparticles, if any, are present in the supernatant, or how much of the supernatant is occupied by proteins and other cellular debris.

Because Knighton produces a therapeutic agent using a different process than the method recited by the pending claims, the reference can not be considered anticipatory (*see, In re Garnero,* 412 F.2d 276, 279, 162 USPQ 221, 223 (CCPA 1979); and M.P.E.P § 2113). Thus, Applicant respectfully requests that the rejection be withdrawn.

U.S. Patent No. 5,185,160 to Chao as evidenced by Exner et al., 2003, Blood Coagulation and Fibrinolysis, 14:773-9

Claims 17-21 stand rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,185,160 to Chao (hereafter, "Chao") as evidenced by Exner et al., 2003, Blood Coagulation and Fibrinolysis, 14:773-9 (hereafter, "Exner"). The Examiner contends that Chao describes a pharmaceutical composition for treating wounds comprising microparticles released from platelets that have been activated by repeated freezing and thawing, wherein the microparticles have been separated from the platelets by centrifugation, and further, have been subjected to virus inactivation by heat. The Examiner relies on Exner for disclosure that freezing-thawing activates platelets. According to the Examiner, the product described by Chao describes the claimed invention.

Applicants respectfully disagree. Chao does not anticipate the pending claims because the reference does not describe all the claim elements. Chao describes "platelet membrane microparticles" that are platelet membrane vesicles with procoagulant activity. *See*, Chao at Col. 2, lines 40-50. Chao produces the vesicles from platelet ghosts whose membranes are disrupted, for example, by repeated freeze-thawing or through hypotonic exposure to glycerol. *See, e.g.,* Chao at Col. 4, lines 17-39. However, to generate microparticles, platelets are needed which are intact, not disrupted thrombocyte ghosts, since the excretion of microparticles by thrombocytes constitutes an active process by the cell. *See*, e.g., Simak and Gelderman, 2006, Transfusion Medicines Reviews. Vol. 20:1-20, cited in the IDS filed 12/7/07, at page 2, "It is important to point out that MP [Microparticle] release is not a random process such as the degradation of the plasma membrane of dying necrotic cells but a highly controlled process associated with different types of cell stimulation." Thus, although Chao may identify its biosubstance as a "microparticle," the biosubstance is produced from disrupted ghost platelets, and as such, is different than the microparticles of the present invention.

In contrast, the thrombocytes of the pending claims are activated by administration of an activating agent selected from the group consisting of thrombin, collagen, calcium ionophore A23187 and C5b-9, such that microparticles are released from the thrombocytes into a liquid medium.

As discussed above, Applicants submit that in product-by-process claims, the process steps should be considered when assessing the patentability of product-by-process claims over the prior art.

> The structure implied by the process steps should be considered when assessing the patentability of product-by-process claims over the prior art, especially where the product can only be defined by the process steps by which the product is made, or where the manufacturing process steps would be expected to impart distinctive structural characteristics to the final product.

*See, e.g., In re Garnero,* 412 F.2d 276, 279, 162 USPQ 221, 223 (CCPA 1979); and M.P.E.P § 2113. The product described by the pending claims is produced by a process that is different than the method of generating a vesicle product from ghost platelets, as described by Chao, and discussed above. Thus, the product prepared according to the process recited by the pending claims is different than the product produced according to Chao's methods. For at least the reasons described above, Applicants assert that Chao is not an anticipatory reference, and respectfully requests that the rejection be withdrawn.

## II. Rejections under 35 U.S.C. § 103(a)

U.S. Patent No. 5,165,938 to Knighton, U.S. Patent No. 5,185,160 to Chao, U.S. Patent No. 5,552,290 to Michelson et al. and U.S. Patent No. 5,697,980 to Otani et al.

Claims 17-26 stand rejected under 35 U.S.C. § 103(a) as being obvious over Knighton, Chao, U.S. Patent No. 5,552,290 to Michelson et al. (hereafter, "Michelson") and U.S. Patent No. 5,697,980 to Otani et al. (hereafter, "Otani"). The Examiner contends that Knighton and Chao disclose compositions comprising microparticles, as described above. The Examiner now relies on Otani for its alleged disclosure of filling and prosthetic devices made of titanium, calcium phosphate and organic polymers. The Examiner also relies on Michelson for its purported disclosure that knowledge about the use of various platelet activating agents for making and collecting platelet derived microparticles is available in the prior art as adequately demonstrated. According to the Examiner, it would have been obvious to add the microparticles of Knighton and Chao to the medical devices of Otani for the purpose of creating a device for

wound healing. Thus, according to the Examiner, the combined disclosure of the cited references describes the claimed invention.

Applicants respectfully disagree. To support an assertion of obviousness, the Examiner must show that "all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art." M.P.E.P § 2143. *See also KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 127 S. Ct. 1727, 82 (2007).

Applicants submit that the claims are not obvious over the cited references because the combined disclosure of the cited references does not describe all the elements of the pending claims, and as such, an artisan of ordinary skill, in view of the combined disclosure of the cited references, would have no reasonable expectation of successfully practicing the claimed invention. As discussed previously, neither Knighton nor Chao suggests or describes a composition comprising microparticles prepared by, among other steps, separating the microparticles from an aqueous fraction of a thrombocyte-free liquid medium, as recited by the pending claims. Neither of Michelson nor Otani disclose microparticles as described by the pending claims. As such, combining the disclosures of Michelson and Otani with the disclosures of Knighton and Chao does not rectify the failure of Knighton and Chao in describing the claimed invention. For at least this reason, the claims are not obvious over the combined disclosure of the cited references, and Applicants respectfully request that the rejection be withdrawn.

## III. CONCLUSION

In view of the above amendments and remarks, it is respectfully requested that the application be allowed and passed to issue. If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below. Applicants believe that no fee in addition to the fees associated with the Petition to extend time and the Request for Continued Examination are due at this time. However, if any other fees are required, the Commissioner is authorized to charge such fees to Deposit Account No. 02-4377.

Respectfully submitted,
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